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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/617,923	07/17/00	GLIMCHER L	HUI-026DV2

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HM22/1002

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1644	7

DATE MAILED: 10/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

UNITED STATES DEPARTMENT OF COMMERCE
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 7/17/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 33-36 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 33-36 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 10/13/00
☑ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644, Technology Center 1600.

2. Applicant's preliminary amendment, filed 7/17/00 (Paper No. 2), has placed this application in compliance with the sequence rules for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

Applicant is required to amend the specification (e.g. Brief Description of the Drawings) to indicate the appropriate SEQ ID NOS.

3. Applicant's amendment, filed 7/17/00 (Paper No. 2), has been entered.
Claims 1-32 and 37-44 have been canceled.

Claims 33-36 are pending and being acted upon presently.

4. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

5. Applicant's submission of an IDS, filed 10/13/00 (Paper No. 3), is acknowledged.
However, the parent applications were not available to the examiner at this time and therefore the references were not considered at this time.

6.The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

7. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

8. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 33-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection

The specification does not provide adequate written description of the claimed invention, namely, "NIP45 protein", other than that set forth in SEQ ID NO: 2 or encoded by SEQ ID NO: 1, as disclosed in the instant specification as-filed because the relevant identifying characteristics such as structure or other physical and/or chemical characteristics are not set forth in the specification as-filed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant is claiming a generic class of molecules, namely NIP45 proteins as the targeted specificity of the claimed antibodies based upon the support of the disclosure of a limited representative number of species, encoded by SEQ ID NO: 1 or set forth in SEQ ID NO: 2. The instant invention encompasses any NIP45 protein, yet the instant specification does not provide sufficient written description as to the critical or identifying structural features of said NIP45 proteins and the correlation between the chemical structure and the desired structural and/or function. The reliance on the disclosed limited example of a particular NIP45 protein specificity does not support the written description of any NIP45 protein.

It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus an assignment of function based upon sequence homology or identity without further functional analysis does not appear to provide sufficient written support for the claimed NIP45 specificity, other than that disclosed in the specification as-filed.

The instant claims do not provide functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus can be highly variable, the disclosure of SEQ ID NOS: 1 and 2 are insufficient to describe the genus of any NIP45 protein, encompassed by the claimed antibody specificities.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus of NIP45 proteins , one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

With the exception of SEQ ID NOS: 1 and 2 disclosed in the specification as filed; the skilled artisan could not envision the detailed chemical structure encompassed by the claimed any NIP45 protein that the the target of the claimed specific antibodies at the time the invention was made and based upon the specification as filed. Applicant has failed to provide sufficient written description for all of the "NIP45 proteins" specifically bound by the claimed antibodies.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. Claims 33-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "NIP45 protein" set forth in SEQ ID NO: 2 or encoded by SEQ ID NO: 1, does not reasonably provide enablement for any "NIP45" protein" as the claimed antibody specificity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies NIP45 proteins other than those encompassed by SEQ ID NOS. 1 and 2 . While NIP45 protein may have some notion of the activity of the claimed protein, claiming biochemical molecules by a particular name given to the protein fails to distinctly claim what that protein is and what it is made up of. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any NIP45 protein other than those defined by SEQ ID NOS. 1 and 2.

The specification does not provide a sufficient enabling description of the claimed invention, including the nucleic acids encoding the particular Toll homolog encoding nucleic acids set forth in Figure 12 or in SEQ ID NO: 13 and that provided by the Clone ATCC Accession No. 209431 as well as for a polynucleotide sequence with at least 95% / 80% identity with the nucleic acid sequence disclosed in Figure 12, over its entire length or that hybridize to said sequences.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Besides the NIP45 proteins defined by SEQ ID NOS: 1 and 2, the specification fails to provide sufficient guidance and direction as to how to make or use the claimed NIP45 proteins, broadly encompassed by the claimed invention.

A person of skill in the art is not enabled to make and use NIP45 as broadly encompassed by the claimed invention. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance based on the disclosure of the instant specification to direct a person of skill in the art to select or to predict particular sequences as essential for in defining the structural and functional characteristics of a NIP45 protein and, in turn, defining antibodies that are specific for said NIP45 protein.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus an assignment of function based upon sequence homology or identity without further functional analysis does not appear to provide sufficient enabling support for the claimed Toll homolog encoding nucleic acids and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

A person of skill in the art is not enabled to make and use NIP45 as broadly encompassed by the claimed invention. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance based on the disclosure of the instant specification to direct a person of skill in the art to select or to predict particular sequences as essential for in defining the structural and functional characteristics of a NIP45 protein and, in turn, defining antibodies that are specific for said NIP45 protein.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects NIP45 and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological and pharmacological activities.

Because of the lack of sufficient guidance and predictability in determining which modifications would lead to defining the structural and functional characteristics of NIP45 and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of NIP45 proteins and, in turn, antibodies specific thereto.

The genus encompasses antibodies that can bind NIP45 protein wherein such NIP45 proteins could encompass have numerous differences in amino acid sequences, including numerous differences in linear and conformational epitopes.

However, the present specification fails to provide sufficient disclosure of such NIP45 proteins that maintain the structural and functional properties of the NIP45 protein encompassed by SEQ ID NOS: 1 and 2. The specification does not provide sufficient guidance as to which of the amino acids may be changed while NIP45 structural or functional activity and specificity is retained.

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the limited disclosure of NIP45 protein's role in cytokine gene expression accurately reflects the relative ability or efficacy of the claimed pharmaceutical compositions of NIP45-specific antibodies.

Page 24, paragraph 2 of the instant specification (IV. Pharmaceutical Compositions) provides a limited disclosure that the claimed pharmaceutical compositions can be used as antibacterial or antifungal agents.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint including antibacterial or antifungal endpoints by administering anti-NIP45 antibodies. The specification does not teach how to extrapolate data obtained from the in vitro Examples disclosed in the instant specification to the development of effective NIP45-specific antibody compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the ability of the efficacy of the claimed anti-NIP45 antibodies to serve as antibacterial or antifungal agents, encompassed by the claims.

Therapeutic administration of a protein that functions as instant intracellular targets would face the additional challenge that, even if it is successfully targeted to a cell, the protein must still be internalized across the plasma membrane, and be able to gain access to the nucleus. In addition, the consequences of in vivo administration of an antibody that would be able to selectively target an intracellular molecule are unknown and unpredictable, and without highly selective targeting to the intended cell population could result in inappropriate activation or modulation of an immune response. Further, it has been well known in the art by the skilled artisan at the time the invention was made that there are distinct differences in the regulation for particular types of inflammation.

Manning et al. disclose that pharmaceutical or anti-inflammatory agents may work by modulating gene expression, however cell-specific inhibitors or candidates are limited by pleiotropic effects and the need to reach intracellular targets and the need to elucidate regulatory pathways (see Inflammation: Basic Principles and Clinical Correlates, 3rd ed., edited by John I. Gallin and Ralph Snyderman. Lippincott Williams & Wilkins, Philadelphia ~~199~~ 1999, pages 1159-1176).

Peltz (Current Opinion in Biotechnology 8: 467-473, 1997) discloses that there is a lack of information about critical elements controlling transcription factor regulation and the factors controlling the cellular response to activation and that the relative importance of recently identified factors has yet to be determined (see entire document, including Conclusions)

It is noted that Manning et al. and Peltz do not disclose antibodies to intracellular targets such as NIP45 are potential inhibitors.

Further, the instant disclosure is drawn to the use of NIP45-specific antibodies to act as antifungal or antibacterial agents in the absence of sufficient objective evidence that such antibodies would be able to achieve such goals

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective pharmaceutical compositions comprising antibodies to target intracellular targets including the ability to treat bacterial or fungal infections, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed pharmaceutical compositions are effective for inhibiting bacterial or fungal infections.

13. Claims 33-36 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 33-36 are indefinite in the recitation of "NIP45 protein" in that they only describe the antibody specificity of interest by an arbitrary protein name. While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein. Applicant should particularly point out and distinctly claim the "NIP45 protein" by claiming sufficient characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of. The claim does not delineate what is to be included or excluded from the claimed subject matter and what the metes and bounds of NIP45 protein are to be.

B) Claim 35 lacks proper antecedent basis to the antibody of claim 33, given that the claim 35 is conjugated or labeled antibody and claim 33 is not a conjugated or labeled antibody.
Applicant is invited to submit claim 35 with the appropriate preamble or recitation to obviate this rejection.

C) Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

14. No claim is allowed.

The instant NIP45-specific antibodies, wherein NIP45 is set forth in SEQ ID NOS: 1 and 2 appears free of the prior art.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
September 28, 2001